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Investigation of Heschl's gyrus and planum temporale in patients with schizophrenia and bipolar disorder: A proton magnetic resonance spectroscopy study

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ABSTRACT

Background: Superior temporal cortices include brain regions dedicated to auditory processing and several lines of evidence suggest structural and functional abnormalities in both schizophrenia and bipolar disorder within this brain region. However, possible glutamatergic dysfunction within this region has not been investigated in adult patients.
Methods: Thirty patients with schizophrenia (38.67 ± 12.46 years of age), 28 euthymic patients with bipolar I disorder (35.32 ± 9.12 years of age), and 30 age-, gender- and education-matched healthy controls were enrolled. Proton magnetic resonance spectroscopy data were acquired using a 3.0 T Siemens MAGNETOM TIM Trio MR system and single voxel Point REsolved Spectroscopy Sequence (PRESS) in order to quantify brain metabolites within the left and right Heschl's gyrus and planum temporale of superior temporal cortices.
Results: There were significant abnormalities in glutamate (Glu) ($F(2,78) = 8.52$, $p < 0.0001$), N-acetyl aspartate (tNAA) ($F(2,81) = 5.73$, $p = 0.005$), creatine (tCr) ($F(2,83) = 5.91$, $p = 0.004$) and inositol (Ins) ($F(2,82) = 8.49$, $p < 0.0001$) concentrations in the left superior temporal cortex. In general, metabolite levels were lower for bipolar disorder patients when compared to healthy participants. Moreover, patients with bipolar disorder exhibited significantly lower tCr and Ins concentrations when compared to schizophrenia patients. In addition, we have found significant correlations between the superior temporal cortex metabolites and clinical measures.
Conclusion: As the left auditory cortices are associated with language and speech, left hemisphere specific abnormalities may have clinical significance. Our findings are suggestive of shared glutamatergic abnormalities in schizophrenia and bipolar disorder.

1. Introduction

Emil Kraepelin's dichotomous approach to discriminate schizophrenia and bipolar disorder relies on their different clinical courses. However, there has been discrepancy between Kraepelin's approach and studies showing co-aggregation of schizophrenia and bipolar disorder in families as well as shared susceptibility genes (Bramon and Sham, 2001; Craddock and Owen, 2005). The challenge arises due to the presence of overlapping symptoms between schizophrenia and bipolar disorder, but yet the desire for clear diagnostic categorization. Dimensional concepts suggest focusing on symptom domains rather than diagnostic categories (Cuthbert, 2014; Keshavan and Ongur, 2014). These symptom domains in conjunction with biological findings may provide insight for shared and distinct mechanisms underlying the disorders.

Superior temporal cortices host primary, secondary and association auditory cortices and have been implicated in the pathophysiology of

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schizophrenia. Both postmortem and in vivo measurements have shown reductions in volume, thickness and gray matter content of the superior temporal cortex in schizophrenia (Vita et al., 2012; Modinos et al., 2013). Longitudinal studies report progressive gray matter loss in the superior temporal gyrus and more precisely the Heschl's gyrus and planum temporale with progression to psychosis and development of delusions (Vita et al., 2012). Moreover, left superior temporal cortices have been associated with symptom domains such as auditory hallucinations (Dierks et al., 1999; Jardri et al., 2011; Kuhn and Gallinat, 2012; Modinos et al., 2013; Shinn et al., 2013) and thought disorder (Seese et al., 2011; Shenton et al., 1992) in psychosis. These findings suggest the superior temporal gyrus as a highly relevant location for the neurobiology and development of psychosis (Shenton et al., 1992; Rajarethinam et al., 2000; Takahashi et al., 2006; Seese et al., 2011). On the other hand, two meta-analyses of volumetric studies of superior temporal cortices did not report any significant differences between patients with bipolar disorder and healthy participants (Kempton et al., 2008; Arnone et al., 2009). However, primary and secondary auditory cortices are located in the region and functional studies consistently reported auditory processing disturbances in both schizophrenia (Dierks et al., 1999; Umbricht and Krljes, 2005; Domjan et al., 2012) and bipolar disorder (Hall et al., 2009; Oribe et al., 2010).

Since glutamate is the major excitatory neurotransmitter and since the EEG signal consists of excitatory end synaptic potentials, auditory processing deficits detected in both schizophrenia (Umbricht and Krljes, 2005; Oribe et al., 2010) and bipolar disorder (Hall et al., 2009; Ethridge et al., 2012; Atagun et al., 2014) could potentially be due to glutamatergic dysfunction in the auditory cortices (Javitt, 2009). Glutamate-modulating agents have been found to be efficacious in the treatment of mood disorders both in pre-clinical (Skolnick et al., 2009) and clinical studies (Sanacora et al., 2008; Machado-Vieira et al., 2012). Current psychotomimetics also modulate different components of the glutamatergic system (for reviews: (Machado-Vieira et al., 2012; Sanacora et al., 2008)). Chronic treatment with lamotrigine, valproate or lithium is likely to effect glutamatergic system through a variety of mechanisms (for reviews: (Colla et al., 2009; Gigante et al., 2012; Schifitto et al., 2009; Soeiro-de-Souza et al., 2013; Yatham et al., 2009)). Therefore, the nature and extent of the glutamatergic system abnormalities in patients with schizophrenia and mood disorders require further clarification.

Proton magnetic resonance spectroscopy (^{1}H MRS) is a non-invasive neuroimaging technique that can quantify in vivo neurochemical metabolites, including those related to the glutamatergic system. Glutamatergic neurotransmission is thought to be disturbed in both schizophrenia (Goff and Coyle, 2001; Paz et al., 2008; Javitt, 2009, 2010) and bipolar disorder (Sanacora et al., 2008; Machado-Vieira et al., 2012). Moreover, altered glutamatergic metabolites have been reported both in schizophrenia (Brugger et al., 2011; Marsman et al., 2013; Poels et al., 2014a,b) and bipolar disorder (Yildiz-Yesiloglu and Ankerst, 2006; Moore et al., 2007; Yuksel and Ongur, 2010; Ongur et al., 2011). Frontal, anterior cingulate and hippocampal regions are the most frequently studied brain regions and the findings were consistent across these brain regions. Only one study has investigated brain metabolites within the superior temporal gyrus (Seese et al., 2011) and reported a correlation between N-acetyl aspartate (NAA) concentrations and thought disorder in children with schizophrenia. However, to our knowledge, no single ^{1}H MRS study has investigated the superior temporal region and compared the findings in adult patients with schizophrenia and patients with bipolar disorder.

Hence, in this study, we utilized ^{1}H MRS to examine neurometabolic changes within superior temporal cortices of adults with schizophrenia or bipolar disorder. Studies by different research modalities consistently report structural and functional abnormalities of auditory cortices, thus we expected to see abnormalities within the neurochemical profile of this region in schizophrenia and/or bipolar disorder.

2. Methods

2.1. Participants and study procedures

Thirty-five stable patients with paranoid schizophrenia (male or female; between ages of 18–59 years old) and 37 euthymic patients with bipolar disorder (male or female; between ages of 20–54 years old) were recruited for the study from the outpatient unit of Ankara Ataturk Training and Education Hospital, Ankara, Turkey. Five of the schizophrenia and 3 of the bipolar patients could not attend the MRI session and hence were excluded. Moreover, 5 of the bipolar patients had bipolar disorder II and therefore were not included in the analysis and we could not acquire neuroimaging data from 1 of the bipolar patients due to technical issues. In addition, 30 age-, gender-, and education-matched healthy participants (male or female; between ages of 18–58 years old) were enrolled in the study. All participants provided written consent upon receiving detailed information about the study. The Ethical Committee of Yıldırım Beyazıt University approved the study.

All participants underwent a clinical interview administered by a psychiatrist (MIA) and diagnoses were checked with the Structured Clinical Interview according to the DSM-IV (SCID-I) (First et al., 1996). The clinical interview assessed the participants' demographics and medical/psychiatric history. Patients with bipolar disorder were evaluated using the Young Mania Rating Scale (YMRS) (Young et al., 1978) and the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). Schizophrenia patients were evaluated with Scale for the Assessment of Positive Symptoms (SAPS) (including subscores for delusion and hallucination) (Andreasen, 1984) and Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983). All patients were also evaluated with the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) and the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971). All participants were free of any brain damage/surgeries or metabolic systemic diseases such as diabetes mellitus or hypertension or current or lifetime psychiatric comorbidity or substance abuse. Psychotropic medications except for benzodiazepines were allowed. Exclusion criteria also included any contraindications to MRI scan. In addition deafness or heading aids were excluded to avoid any possible plasticity effects as a result of hearing disabilities, as we are particularly interested in the temporal lobe. Finally, all participants completed an MRI scanning session.

2.2. NeuroImaging data acquisition

Data were acquired on a 3.0 T Siemens MAGNETOM TIM Trio whole-body MR system (Siemens, Erlangen, Germany) with a thirty two-channel phased-array head coil at the UMRAM National Magnetic Resonance Research Center, Ankara, Turkey.

T1-weighted anatomical MRI (MPRAGE sequence, 256 × 256 voxels, TR: 2000 ms, TE: 3.02 ms, FOV read: 215, FOV phase: 100, slice thickness: 0.84, 192 slices) were collected for diagnostic and localization purposes. Voxels (20 mm × 20 mm × 20 mm) were placed consecutively in the left and right Heschl's gyrus and planum temporale regions (Fig. 1) and proton magnetic resonance spectroscopy (^{1}H MRS) data were acquired using the single voxel Point REsolved Spectroscopy Sequence (PRESS) (TE = 30 ms, TR = 2000 ms, 128 averages) in order to quantify brain metabolites (Fig. 1). Manually adjusted B_0 shimming was applied around the voxel as implemented on our MR system.

2.3. NeuroImaging data analysis

The proton spectra were fit using LCModel (Version 6.3.0) to quantify the metabolite concentrations. LCModel analyzes in vivo proton spectra as a linear combination of model in vitro spectra from individual metabolite solutions (Provencher, 1993, 2001) by utilizing built-in (simulated) radial basis sets. The basis set used for this study included alanine, aspartate, creatine (Cr), phosphocreatine (PCr), γ-aminobutyric acid (GABA),